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Abstract: The diagnosis and treatment of children and adolescents with cancer has a tremendous and lasting effect on the patients, their families, and other individuals in their social network. It carries a host of psychological and neurobehavioral ramifications, from questions of mortality to changes in levels of functioning in multiple domains. Childhood cancer remains the leading cause of illness-related death in childhood, but significant advances in survival have been made in the past 40 years. This review looks at the neuropsychiatric presentations, psychosocial and treatment-related issues that arise in children with brain tumors.

Key words: Paediatric brain tumours, Neuropsychiatric presentations

Background

Psycho-oncology addresses the two major psychiatric and psychological dimensions of pediatric cancer; first, the psychiatric comorbid disorders and psychological responses of children at all stages of illness and their families and, the psychological stresses on health professionals delivering their care; and second the psychological, behavioural, and social factors that influence cancer risk, detection, and survival. (1) Though pediatric cancers constitute a very small portion of the total cancers diagnosed, accounting to only 2% of the total cancers, they remain one of the leading causes of illness related death in

childhood. (2) Brain tumors constitute the second most common tumors in the pediatric age group after the leukemias. (3) Pediatric brain tumors are not similar to adult tumors. Meningioma, malignant gliomas, schwannomas and pituitary tumors are common in adults; however these tumors are rare in children. (4-5) In children more than 50% of the brain tumours are infratentorial and the common tumours are low grade gliomas and primitive neuroectodermal tumours. (6-7) Gliomas represent 45 – 50% of all the pediatric primary brain tumors and are by far the commonest of them. (8) To appreciate the experience of a child who has cancer it is helpful to have an understanding of

the treatments involved. Treatment of pediatric cancer may involve chemotherapy, radiation, surgery, or stem cell/bone marrow transplant, or some combination of these modalities. In contrast, children with primary CNS malignancies, the second most common cancer of childhood, may have surgery only (eg, children with a pilocytic astrocytoma) or have surgery, radiation, and intensive chemotherapy (eg, children with medulloblastoma). (9)

Significant advances in treatment of pediatric brain tumors had influenced the survival rate in the past 40 years. The overall 5-year survival rate for 0- to 16-year-olds diagnosed between 1975 and 1979 was 62.9%, compared with 81.5% in 2005.9-10 Much of this progress has come from the collaboration of pediatric oncology researchers and clinicians. The Children's Oncology Group (COG), supported by the National Cancer Institute, creates standardized treatment protocols for pediatric cancers and then analyzes the responses to care and disseminates this information to all pediatric cancer providers. (11) The degree of emotional expressiveness in children with brain tumor (s) and its possible effect on prognosis have been the subject of interest of a large body of literature. Few descriptive case reports noted shorter survival both in adolescent and adult patients with depressed, resigning attitude compared with patients who were able to express more negative emotions, such as anger. (12) Other clinical and epidemiological studies have not supported such an influence in cancer risk or in cancer mortality. (13) This review looks at the neuropsychiatric

presentations, psychosocial and treatment-related issues that arise in children with brain.

Neuropsychiatric Presentations:

Brain tumours can be either supratentorial or infratentorial depending upon whether they arise from above or below the tentorium. The subjects having tumours in the supratentorial space manifest convulsions more frequently, whereas subjects having tumours in the infratentorial space manifest problems related to balance, posture and cranial nerve functions. Interestingly, morning headaches, nausea, and lethargy resulting from tumour obstruction of the ventricles and raised intracranial tension are some of the common presentations of both of them. (14) Neuropsychiatric presentations in children with brain tumour commonly changes over the course of illness and depends on medical, psychological and social factors: the disease itself (i.e., site, symptoms, clinical course, side effects of chemotherapeutic agents or radiations); prior levels of adjustment; the threat that cancer poses to attaining age appropriate developmental tasks and goals; cultural, religious and spiritual attitude; presence of emotionally supportive persons or caregivers; the potential for psychological and physical rehabilitation; and finally child's temperament and coping style as well as prior experience with loss. (15) Unlike in adults with brain tumours in whom the wide spectrum of neuropsychiatric presentations are being reported the focus in pediatric age group has been largely on issues of adjustment, emotional and mood disorder and cognitive impairment. Let us discuss issues related to adjustments.

Adjustment problems:

Similar to any other significant stressor, child has problems in adjusting himself to the truth of having a critical illness such as brain tumour. Pediatric patients who survive brain tumors cope with the direct physiological insult caused by the tumor itself, the treatments (neurosurgery, chemotherapy, and/or high dose central nervous system irradiation) and treatment related sequelae (e.g., impaired health, extensive school absence, familial stress). Coping of these psychological problems may be different for children of different age group. In preschool age, the child is mostly occupied with magical thinking and believes that he suffering from any chronic illness is a punishment given to him for some trivial wrong deeds. As the preschool children spend most of the time with their family, separation from them for the purpose of the treatment can be very traumatic to the child. In school, the child may face disrupted functioning and problems with peer relationship. This social sequelae can be handled by involving child in activities such as board games, computers etc., and educational help can be provided by offering school tutors. It's not until adolescence, that the child is able to understand the complexity of the chronic illness. (16) The common distresses that the teenager experiences after being diagnosed of cancer are "loosing hair", "missing leisure activities", "fatigue", "pain from procedures and treatment" and "worry about missing school". (17) In adolescence, the patients are not able to form intimate relationships as a result of negative self-image and pessimistic attitudes. This adds to their loneliness and

restricted availability of coping resources. Both of these are challenged during treatment because of feelings of being different and physical appearance changes such as hair loss caused by chemotherapy or weight gain caused by corticosteroids. As a result of low self-esteem and body image concerns expressed by adolescents with cancer, they avoid or are less likely to establish intimate relationships. (18) Future concerns about fertility, threatened by cancer treatment, is also a prominent issue. Semen cryopreservation is available for boys but there are no definitive preservation methods available for girls. (19) These psychological adjustment problems make the children with brain tumors susceptible to various psychiatric illnesses such as mood disorder and anxiety disorder.

Emotional/ Anxiety/Mood disorders

One might assume that a severe stressor such as a diagnosis of cancer during childhood would overwhelm an individual's ability to cope emotionally and most if not all children would experience emotional difficulties. However, studies suggest that most children with cancer do not exhibit significant levels of depression or anxiety, although a significant minority do experience marked levels of psychological distress. (20–23) Some clinical observations have indicated that a subset of patients exhibit more problems, such as greater difficulty coping. (22) Other studies show the emotional well-being of children with cancer currently receiving chemotherapy to be remarkably similar to case-control classroom peers, (23) and initial studies of cancer survivors similarly failed to find increases in social and emotional problems in

children with cancer, (24) although new data on survivors has challenged this view.

In assessing a child's mood, the clinician must be knowledgeable about the side effects of the treatments, which may include fatigue, decreased appetite, and disturbed sleep. If a child does present with clinically significant depressive symptoms, the treatment follows the same course as it would in the physically well child; that is, with psychotherapy such as cognitive-behavioral therapy (CBT) and antidepressant medication as indicated. (25) Although no large studies have been conducted in children with cancer, selective serotonin reuptake inhibitor (SSRI) medications are the pharmacologic antidepressant treatment of choice, as they are in the population at large. (26) In an uncontrolled pilot study of 15 children with cancer and depression or anxiety, fluvoxamine was well tolerated and effective. (27) In another small study, 7% of children involved in National Institutes of Health (NIH) research trials for cancer were found to have been prescribed antidepressant medication. (28) The investigators of this study noted increasing acceptance for psychopharmacologic treatment of subthreshold psychiatric disorders to improve quality of life, and concluded that in addition to psychological support always being indicated in the setting of anxiety or depression, there is a role for the judicious use of psychotropic medications.

The child with cancer often presents to mental health treatment with anticipatory anxiety and/or nausea and vomiting. There are no documented incidence or prevalence studies on particular or specific type (s) of

anxiety spectrum disorders developed after brain tumors. However, anticipatory anxiety without nausea or vomiting component is initially addressed with behavioral interventions. The child may feel nauseated or vomit on arriving at the outpatient clinic or hospital. One study reports 59% of children experienced mild to severe anticipatory nausea and vomiting despite the use of ondansetron. (29) In mild cases, the effective behavioral approaches include thought stopping, hypnosis, distraction, and relaxation. (30) More severe cases of such typified presentations in association with post-chemotherapy nausea and vomiting may respond to increased use of antiemetics, including higher doses of ondansetron, corticosteroids, and benzodiazepines. There are also some data to support the use of acupuncture in this population. (31)

Treatment related issues:

In the psychiatric evaluation and treatment of children with cancer, several prominent areas of difficulty related to cancer treatment emerge, and include psychiatric effects of chemotherapeutic agents, neurocognitive effects of treatment from chemotherapy and cranial radiation, and issues related to adherence with treatment. For the sake of understanding, the neuropsychiatric adverse effects of most commonly prescribed and reported drugs viz. corticosteroids and interferon are discussed below.

Corticosteroids

Corticosteroids are routinely used for the treatment of childhood cancers and their sequelae. In many chemotherapy protocols, including leukemias and lymphomas,

corticosteroids play a central role. The appearance of adverse psychiatric symptoms is common in children who are receiving high-dose corticosteroids. These symptoms include changes in mood, sleep, and appetite. Research in the area of psychiatric adverse effects to corticosteroids is much more extensive in adults than in children. The adult literature supports the role of corticosteroids in causing behavioral changes including depression, mood elevation, irritability, anger, insomnia, and excess talkativeness. (32–34) Psychiatric sequelae are usually dose-dependent and studies have reported increased severity of psychiatric symptoms with higher doses of corticosteroids. Patients can become severely depressed, manic, psychotic and/or delirious. In the largest study of its type, severe psychiatric reactions were seen in 1.3% of patients receiving prednisone 40 mg per day or less; in 4% to 6% of patients receiving 41 to 80 mg per day; and in 18.4% of patient receiving more than 80 mg per day. (35) The use of corticosteroids in children has been studied in children with renal, pulmonary, and gastrointestinal diseases more commonly than in children with cancer and reviewed extremely well by Satel. (36) Effects seen in children with cancer are consistent with the behavioral changes seen in children with other illnesses and in the adult population. In children receiving prednisone at a dosage of 60 mg/m²/d for leukemia and lymphoma, increased irritability, argumentativeness, tearfulness, reports of “talking too much,” tiredness, low energy, and night waking were common symptoms, with a trend toward more symptoms in younger children. (37) In

children with ALL, groups receiving prednisone 40 mg/m²/d and 120 mg/m²/d showed adverse changes in attention/hyperactivity, emotionality, sleep disturbance, depressed mood, listlessness, and peer relations, although there was no significant difference between the two steroid groups. (38) In a few cases, the severity of a child’s depression or mania or the development of psychosis requires a reduction or discontinuation of the corticosteroids as well as acute psychopharmacologic intervention. For mild forms of depression, psychotherapeutic strategies can be beneficial. Psychoeducation for patients and families that symptoms may be transient and biochemically mediated rather than the result of a sudden giving up or self-pity is essential. (39)

Neurocognitive deficits

Apart from adjustment problems and emotional disorders in children, neurocognitive deficits are of a great concern and interest in subjects of brain tumours and their incidence is found to be unacceptably high. The incidence is variable with some reports stating it to be present in more than 50% of paediatric cancers (2), whereas some reports put it at 40% – 100% among long term brain survivors (40) and some go on to state that impaired intelligence is present in 90% of conventionally treated medulloblastoma patients. (41) Despite the differences between ALL and malignant brain tumors, there are significant similarities among the symptoms comprising neurocognitive deficits, particularly with regard to the treatments of brain irradiation and intrathecal chemotherapy. While a considerable body of

evidence has accumulated on the nature of white matter damage from those treatments, variations in tumor pathology and combined treatment protocols over time have made the need for further research necessary. In order to summarize our understanding of the neuropsychological impact of childhood cancers and their treatment, we have chosen to define core deficits, which involve executive functions, processing, and fluid abilities, and secondary deficits, which are knowledge based and oftentimes referred to as crystallized abilities. In the current conceptualization, it is the detrimental effects of cancer and cancer therapy on the biological substrates of core abilities that eventually result in more observable secondary deficits. Several excellent reviews are available supporting this approach to understanding neurocognitive deficits among children surviving brain tumors (42), suggesting that children surviving brain tumors are at greater risk for more severe deficits because of the increased aggressiveness of their therapy and, in particular, the continued use of CRT. While the late effects of CRT typically emerge within 1 to 2 years of administration, there is evidence that brain-damage effects may be delayed up to 7 years. (43) Children who survive a brain tumor do appear to be at risk for social difficulties following cessation of treatment, perhaps due to increased severity of neurocognitive injury. (44) These core and secondary symptoms of neurocognitive deficits may also impact other areas of functioning, such as social interactions. The major core neurocognitive deficits and risk

factors among children treated for malignant brain tumors.

Premorbid factors

The occurrence of neurocognitive deficits depend on various premorbid factors such as female sex, younger age at treatment, genetic polymorphisms, and population and social risk factors. (45) As compared to older counterparts, a younger age at treatment consistently shows a significantly greater decline in age-adjusted scaled scores of intellectual functioning over time. In couple of the studies by same author, the subjects of medulloblastoma who were younger (<8.85 years) experienced more neurotoxicity, when measured on tests of intellectual functioning, than those who were older at treatment (>8.85 years). (46-47) Similar findings were reported demonstrating significantly greater declines in age-adjusted scaled scores of factual knowledge and nonverbal abstract thinking as well as an overall estimate of full-scale IQ in younger subjects receiving radiation treatment for medulloblastoma. (48) Like younger age, female gender also correlated with poorer neurocognitive functions as compared to males having solid brain tumors when measuring for intellectual and academic functioning, including a test of reading comprehension. (49) Moreover in comparison to males, early age of diagnosis and low social economic status were associated with more severe cognitive impairment in females. (50) Other pre-morbid factors predicting the neurocognitive deficits in paediatric subjects of brain tumours are genetic polymorphisms, and population and social risk factors. (51-52)

Sources of neurocognitive deficits

Neurocognitive deficits can occur by myriad of causes ranging from primary CNS tumour effects, neurosurgical sequelae, raised intracranial tensions, seizures and antiepileptic treatments, cranio-spinal radiotherapies and systemic and CNS focused chemotherapies. (53) The growing tumour as well as the raised intracranial pressure occurring mostly as a result of obstructive hydrocephalus causes compression of tissue at both local and remote sites. Hydrocephalus is involved with problems of neurocognitive functioning including memory, attention and perceptual performance. (54) One study demonstrated an association between presence of hydrocephalus and a higher risk for intellectual deficits in paediatric brain tumour subjects. (55) However early correction of hydrocephalus may result in no lasting effect on cognitive functioning. (56) Similarly extent of resection in neurosurgery has also been associated with deficits in intellectual functioning with higher decline associated with more extensive resection. (57) Posterior fossa syndrome (mutism, ataxia and behavioural changes), developing after surgery has a higher risk for neuropsychiatric sequelae. (58, 59) Further studies demonstrated that the surgical resection of brain tumours without adjuvant therapy was itself associated with deficits in neuropsychological testing in attention, memory, processing speed, and visuospatial processing, and a variety of behavioral problems. Moreover other factors such as shunt infections, meningitis or the need for repeat surgery further increased the risk of cognitive decline. (60, 61) Exposure to

cranial radiotherapy while getting treated for brain tumours has also shown to be responsible for the cognitive decline. It is postulated to cause greatest damage to developing white matter and as a result has been shown to cause the greatest negative sequelae for the developing brain. Myelination normally continues after birth into the third decade of life (62) and exposure to CRT can disrupt this developmental process, ending in demyelination, and ultimately white matter damage. In addition, immature oligodendrocytes are thought to be more vulnerable to injury than the mature counterparts. (63) Treatment with cranial radiotherapy has shown to reduce the IQ by 15 to 25 points in children with brain tumors. (64, 65) In view of these findings of significant cognitive decline, efforts are now shifted to develop new protocols having the advantage of decreasing the radiation exposure while maintaining the same cure rate. These efforts involve using early focal radiotherapy and decreasing the target tissue volume and dose of cranial radiation. (66) Like radiotherapy, chemotherapy with agents such as methotrexate has also shown to cause neurocognitive deficits though not as severe as the former. Methotrexate is known to interfere with folate metabolism resulting in demyelination and other toxic effects on CNS thereby leading to cognitive decline. (67) Problems that are reported with the use of chemotherapy in treatment of pediatric brain tumors are problems with sustained attention, which correlated with teacher reports of poorer academic performance, particularly in mathematics, increased internalizing

behaviors on the Child Behavior Checklist, a parent report measure of social competence and behavior problems, visual processing, visual-motor functioning, attention and executive functioning, academic performance, verbal abilities, and memory with female gender and young age (particularly less than age 3 years) as risk factors. (68-70)

Psychopharmacological and palliative care interventions for neurocognitive effects:

Although the research on the pattern and causes of neurocognitive deficits in pediatric brain tumors has been rapidly progressing over the last few decades, the development of empirically validated treatment for these deficits is still in its infancy. The role of psychiatrists and psychologists in identifying, assessing and dealing with these deficits cannot be underestimated. As in any child with academic difficulties and cognitive impairments, mental health professionals should strive towards educating family members and school personnel about the deficits that are expected to develop as the treatment progresses and also advocating for proper services. The management can be a primary prevention wherein, the CNS insult is tried to be reduced in order to prevent development of neurocognitive deficits. As radiotherapy is known to cause the maximum CNS insult, protocols are using lower doses of cranial radiation, decreasing the tissue target volume, and postponing radiation in the highest risk groups or using early focal radiotherapy to minimize the cognitive effects. (71) Newer forms and techniques for delivering radiation are also being used. For example, proton beam radiotherapy, as

opposed to standard photon radiotherapy, may decrease the likelihood of significant neurocognitive decline, because there is no exit radiation dose thereby decreasing the volume of white matter involved. In addition to morbidity-limiting strategies to minimize the neurotoxic effects (particularly cranial radiation), some investigators have examined interventions for neurocognitive effects after they have occurred. (72, 73) As in any child with academic difficulties and cognitive impairments, mental health professionals working with survivors of cancer have a role in educating family members and schools about deficits seen in this population, and advocating for appropriate accommodations and services. Studies show that the decline in IQ may not be apparent initially and can be progressive over time, highlighting the importance of following children longitudinally. One potentially useful addition to the development of interventions for cognitive deficits has been an appraisal of the influence of the family environment and resources following recovery from traumatic brain injury. The importance of family cohesiveness and stability in recovery from brain injury has long been known. As early as 1958, it was reported that children who suffered a traumatic brain injury and developed psychiatric disturbance had greater degrees of family pathology as those who did not experience a mental disorder. (74) Other researchers have further demonstrated the relationship between family pathology and behavioral difficulties among brain injured children. (75, 76) More recently, Yeates and colleagues (77) (1997) have documented that

chaotic and dysfunctional family environments have a significant adverse impact on neurological and neuropsychological recovery from traumatic brain injury among school-age children. This relationship appears to be valid even when severity of brain injury and other medical factors were experimentally controlled (Max et al., 1999). (78) It appears that family burden, characterized by ratings from parents as to the negative impact of the child's injury on the family, and overall family adjustment are significant predictors of continued neurobehavioral symptoms following childhood traumatic brain injury (Yeates et al., 2001). (79) How might these findings be relevant to survivors of childhood cancer having neurocognitive problems? One could speculate that the family environment might be of equal or greater importance in the treatment and recovery of a chronic life-threatening disease compared with an acute event such as a traumatic brain injury. Certainly, educating parents to be advocates for their children by giving them sufficient information and support should be a component of any clinical intervention. Whether formal training in special skills would facilitate recovery of function among children treated for traumatic brain injury or cancer is not yet known.

Adherence

Adherence a more proactive term than compliance to treatment regimens is a prominent issue with children and adolescents having brain tumors. Adolescents consistently show higher rates of non-adherence compared with children and adults in the treatment of

cancer and other life-threatening illnesses. (80-84) Risk factors for poor adherence with cancer treatment in adolescents have been identified, including low socioeconomic status of the family, (84-86) barriers to communication such as cultural and linguistic differences, (87) and mental illness, including depression in a parent and behavioral disturbances during the patient's childhood. Clinically, poor communication between adolescents and their parents around treatment seems to be a significant contributor to poor adherence. It is important to identify non-adherence issues early in treatment. Blood levels of a drug or its metabolites have been used to monitor adherence with oral medication regimens, such as 6-mercaptopurine in the treatment of ALL. (85,86) A nonjudgmental inquiry about the patient's consistency in taking the medication may be just as effective. (84) Confusion about appropriate doses or about who is responsible for administering the medication may contribute to unintentional non-adherence.

Psychological issues at the end of the life

Although most children with cancer survive, childhood cancer remains the leading cause of illness-related death in childhood and is the second leading cause of death in children, behind accidents. The reality of cancer as a sometimes terminal illness affects patients, families, and caregivers alike. Oncology teams utilize the services of social workers, psychologists, psychiatrists, chaplains, and child life specialists to assist the child, family, and staff with the challenges faced at the end of life. These care providers can facilitate family conversations about death

between parents and with the child. (89) Conversations about dying and end-of-life care are inherently difficult and often avoided, but data support having open conversations with children. Kreicbergs and colleagues (90) found that parents of children with severe malignant disease who had conversations with their children about dying did not regret these conversations.

Children with cancer experience significant physical and psychological symptoms and suffering at the end of life. (91) Despite this, palliative care services are available at only 58% of institutions caring for pediatric oncology patients, highlighting one obstacle to offering optimal care to all children treated for cancer. (92) Many of the difficulties encountered in the terminal phase of children with cancer are common to all children at the end of life. See the article by Knapp and colleagues elsewhere in this issue for further exploration of this topic.

Conclusions

Neuropsychiatric presentations of pediatric brain tumors are both interesting and valuable in the midst of current concerns; interesting because it increases our understanding about presenting patterns and their mechanism of evolution and useful because of the possibility of learning more and better from previous experiences of clinicians. Recent decades have brought about tremendous improvements in survival outcomes for children with cancer. Overall, children with cancer are resilient, but they are confronted with several challenges adjusting to their illness, dealing with treatment related

effects, and for some facing end-of-life care. Children having brain tumours undergo various psychosocial stressors and related psychiatric problems such as mood disorders and neurocognitive deficits which need to be evaluated and assessed longitudinally in every child. These facts make the need that both mental health clinicians and pediatricians should play a critical role in providing the assessment, support, and treatment needed in the childhood cancer population. Continued research in this field is imperative. Incorporation of systematized psychiatric care in the routine management of paediatric brain tumours can improve the quality of life of the patients and make the oncology treatment complete. Continued research in this field is however imperative.

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